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Hypersensitivity pneumonitis: Current concepts and future questions

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Hypersensitivity pneumonitis (extrinsic allergic alveolitis) caused by inhaled allergens can progress to disabling or even fatal end-stage lung disease. The only truly effective treatment is early recognition and control of exposure. Although patients produce antibody exuberantly, the immunopathogenesis involves cellular immunity—notably, $CD8^+$ cytotoxic lymphocytes, multinucleate giant cell granulomas, and ultimately interstitial fibrosis. Many causative agents have been recognized in occupational dusts or mists, but most current new cases arise from residential exposure to pet birds (pigeons and parakeets), contaminated humidifiers, and indoor molds. The symptoms and physical findings are nonspecific. Serum IgG containing high titers of specific antibody to the offending antigen is elevated. Pulmonary function tests show restrictive and diffusion defects with hypoxemia, especially after exercise. Occasionally, small airways disease causes obstruction. Radiographic changes vary according to the stage of the disease and are best evaluated by means of high-resolution computed tomography. In typical cases, the history of a known exposure and the presence of a characteristic interstitial lung disease with serologic confirmation of IgG antibody to the offending antigen suffice for diagnosis. In more obscure cases, observation of changes after a natural environmental exposure, bronchoalveolar lavage, and lung biopsy might be indicated. Among the many questions that remain are the following: What is the prevalence of hypersensitivity pneumonitis and how often is it the cause of chronic interstitial fibrosis? What is the long-term prognosis? Why do most individuals exposed to these antigens develop a vigorous antibody response whereas only a few develop the disease? How does exposure to endotoxin and cigarette smoking affect the disease? To answer these questions, standardized and validated clinical laboratory immunochemical tests are needed, in addition to a systematic approach to diagnosis, classification of disease severity, risk assessment, and management. This review is limited to the disease caused by airborne allergens and focuses on its immunopathogenesis, eliciting agents, clinical manifestations, diagnosis, management, and prognosis. (J Allergy Clin Immunol 2001;108:661-70.)

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Hypersensitivity pneumonitis (HP), also known as *extrinsic allergic alveolitis*, is a chronic disease, often with acute exacerbations, caused by inhaled allergens that elicit lymphocytic inflammation in the peripheral airways and surrounding interstitial tissue. Monocytes soon accumulate and mature into foamy macrophages that develop into granulomas widely dispersed throughout the lung. The end result is interstitial fibrosis with a radiographic appearance of honeycombing. The development of clinically significant disease depends on the type, intensity, and duration of exposure to the inciting agent, the susceptibility of the host, the site of interaction within the respiratory system, and the resulting level of dysregulation of the cellular and humoral immune response over time. The inciting agents can be derived from fungal, bacterial, animal protein, or reactive chemical sources.

Most of the causative allergens have been recognized in a wide variety of occupations; consequently, once the problem has been identified, the exposure can be controlled and the disease prevented. As a result of this reduction in occupational exposures, the disease is now less common than it was 20 years ago. However several issues remain:

1. Important exposures now occur at home; they are especially associated with pet birds, contaminated humidifiers, and heavy concentrations of indoor molds. These residential exposures are more difficult to recognize.
2. The immunopathogenesis in which macrophages and $CD8^+$ cytotoxic lymphocytes play a central role is still incompletely defined. The strong possibility exists that similar immunologic mechanisms are operative in other interstitial lung diseases, such as rheumatoid arthritis and idiopathic pulmonary fibrosis.
3. Many of the environments that cause HP also contain airborne gram-negative endotoxin, the result being fever and cough after acute exposure and chronic bronchitis and emphysema with chronic exposure. As a consequence of this mixed exposure, workers can develop HP, which is a lymphocytic disease, chronic obstructive pulmonary disease, which is a neutrophilic disease, or both.

Abbreviations used
BAL: Bronchoalveolar lavage
HP: Hypersensitivity pneumonitis
HRCT: High-resolution computed tomography
MIP: Macrophage inflammatory protein

The term *hypersensitivity pneumonitis* has become somewhat ambiguous, inasmuch as it is also applied to lung inflammation and fibrosis caused by drugs (such as methotrexate) and is sometimes applied to other inflammatory/fibrotic diseases of unknown cause. This review is limited to the disease caused by airborne allergens and focuses on the immunopathogenesis, eliciting antigens, clinical manifestations, diagnosis, management, and prognosis. It is useful to consider the 3 stages of the disease separately: acute lymphocytic infiltration, subacute granuloma formation, and chronic fibrosis.

IMMUNOPATHOGENESIS

HP is characterized both by proliferation of $CD8^+$ cytotoxic lymphocytes and by an exuberant production of antibody, especially IgG, presumably from proliferation of plasma cells stimulated by $CD4^+$ T_H1 lymphocytes. Both of these pathways begin after inhaled antigen-carrying particles are ingested by macrophages. Unfortunately, many of the details of the cellular interactions that are responsible for the immunopathogenesis of HP are still obscure. Much of the information about these immunologic mechanisms has been derived from animal models, confirmed when possible by study of bronchoalveolar lavage (BAL) fluids and biopsy specimens from patients. Although the immunopathogenesis of the 3 phases of HP overlap, it is convenient to discuss them separately. Not surprisingly, the processes of alveolitis, granuloma formation and fibrosis in many ways resemble those of other diseases, such as tuberculosis, sarcoidosis, and idiopathic pulmonary fibrosis.

A particularly puzzling question is why of all similarly exposed individuals only approximately 1% go on to develop the disease. Most exposed individuals develop what appears to be a normal innocuous IgG antibody response. Antibody alone is not sufficient to cause disease; cytotoxic delayed hypersensitivity involving $CD8^+$ cytotoxic lymphocytes is required. Some patients report that though they had been exposed for years, the symptoms only appeared after a recent acute respiratory infection. It is of interest that in the mouse model, respiratory syncytial virus infection increased granuloma formation and production of IL-8 and INF-γ. However, the factors responsible for development of the more complex immune reaction in human beings remain poorly defined. Patients who developed the disease had greater production of the macrophage cytokine TNF-α and expressed the TNF A2 allele, a genotype associated with high production of TNF-α.[1] Activation of $CD8^+$ lymphocytes requires binding of the T-cell receptor to MHC class I molecules of the antigen-presenting cell, but results of studies attempting to link HP to determinants of the MHC class I locus have been contradictory.[2,3] The $CD8^+$ cells in the lung have increased usage of Vβ regions of the T-cell receptor gene, but no specific genetic basis for the disease has been established.[4-6]

Acute phase: macrophage-lymphocyte response

After inhalation, soluble antigens bind IgG antibody, the immune complexes initiate the complement cascade, and the resulting C5 activates macrophages.[7] As a result of stimulation by C5 or activation by ingestion of antigenic particles, macrophages secrete chemokines and cytokines that first attract neutrophils and after several hours attract and activate not only circulating T lymphocytes but also monocytes. In contrast to IgE-mediated allergic reactions, eosinophilia is rare. Chemokines include IL-8, macrophage inflammatory protein α1 (MIP-1α), and RANTES.[8-11] IL-8 is a chemotactic factor for T lymphocytes as well as neutrophils. Cultured respiratory cells stimulated with the thermophilic actinomycete *Saccharopolyspora rectivirgula* produce IL-8,[12] but the MIPs might be more important. MIP-α1 not only is a chemotactic factor for monocytes/macrophages and T lymphocytes but also promotes the differentiation of $CD4^+$ T_H0 cells to T_H1 cells. MIP-α1 acts as a chemotactic factor for macrophages and lymphocytes.

The cytokine IFN-γ, presumably produced primarily by activated $CD4^+$ T_H1 lymphocytes, is necessary for the activation of macrophages to develop granulomas in a mouse model of HP.[13,14] Cytokines produced by activated macrophages include IL-1 and TNF-α, which cause the fever and other acute phase reactions. In comparison with idiopathic pulmonary fibrosis, macrophages from patients with HP secrete more TNF-α and less IL-1.[15] Furthermore, BAL fluid contains the soluble receptor proteins TNFR1 and sTNFR2.[16] IL-6, another important chemokine from activated macrophages, promotes the differentiation of B cells to plasma cells and maturation of $CD8^+$ cells into cytotoxic cells.[17] IL-12 from stimulated macrophages promotes the development of T_H0 to T_H1 cells. Macrophages from mice sensitized to thermophilic actinomycetes secrete IL-12,[8] and T cells cultured from BAL fluid obtained from patients with HP have increased receptor for IL-12.[18]

Activated macrophages have increased expression of the adhesion molecules CD80 and CD86, and the T cells have increased CD28.[19] CD80/86 (also known as B-7) and its counter ligand, CD28, are essential costimulatory molecules for antigen presentation and also for B-cell activation by $CD4^+$ T-helper cells. Blockade of this ligand system inhibits inflammation in the mouse model of HP.[20] Endothelial adhesion molecules are critical for the inflammatory cells to enter the pulmonary tissue. Inhibition of E- and P-selectins or ICAM-1 blocks the recruitment of lymphocytes.[21] Activated macrophages and lymphocytes not only express CD18/CD11, the ligand for ICAM-1, but also express increased ICAM-1.[22]

Increased numbers of $CD4^+$ T_H1 cells appear in the BAL fluid shortly after exposure, but in most cases of HP $C8^+$ cells predominate later; this is in contrast to sarcoidosis, in which $CD4^+$ cells are dominant.[23] The predominance of $CD8^+$ lymphocytes was not observed in some cases because of isocyanates, however.[24]

Subacute phase: granuloma formation

After recruitment into the lung and activation by monokines, especially MIP-1, the young macrophages develop into epithelioid cells and multinucleated giant cells.[25] The details of the cell biology of this transformation of monocytes into the typical multinucleated giant cells that make up granulomas remain undefined.

Lymphoid follicles containing plasma cells also develop in the lesions during the subacute phase.[26] This is consistent with the proliferation of $CD4^+$ T_H1 lymphocytes bearing the CD40 ligand that is required for the activation of B cells; it also indicates that at least part of the exuberant antibody formation occurs locally in the lung.[27]

Chronic phase: fibrosis

In all of the granulomatous diseases, early collagen formation by myofibroblasts occurs and the extracellular matrix surrounding the granuloma becomes rich in the proteoglycan versican.[28] Activated alveolar macrophages express increased amounts of TGF-β, a potent stimulator of fibrosis and angiogenesis.[29] Expression of the Fas ligand and the CD40 ligand systems are also involved in the development of fibrosis.[30,31] BAL fluid contains increased amounts of vitronectin, fibronectin, and procollagen III peptide, even in the early phase of HP.[32] The concentration of procollagen III peptide correlated with the number of mast cells.[33] Increased numbers of mast cells are present in BAL fluid in both the mouse model and human HP, as well as in other interstitial diseases.[34-38] Mast cell–deficient mice do not develop lung inflammation.[39] Most of the mast cells in BAL fluid from HP have characteristics of the connective tissue type rather than the mucosal type and, being related to fibrosis, might differ in function from the mast cells active in asthma.[40] Although symptoms attributable to histamine do not occur in HP, mast cells are sources of cytokines and likely contribute to both the recruitment and the maturation of monocytes and lymphocytes; they also promote fibrosis.[41] This is consistent with the observation that mast cells, along with lymphocytes, macrophages and plasma cells, are abundant in the interstitial tissue.[42] Neutrophils might also contribute to the fibrosis of HP.[43] The frequent contamination of the environments that cause HP with gram-negative endotoxin might contribute to the neutrophilia and lung disease.[44]

CAUSATIVE AGENTS

Causative agents of HP include microbes, animal and plant proteins, and organic and inorganic chemicals (Table I). Exposure to these airborne antigens occurs in various occupations, hobbies, and environments with contaminated air-handling equipment. A few of these exposures account for the majority of patients with HP. Others have been reported only in isolated cases. These isolated cases illustrate the importance of the careful taking of an environmental history. Furthermore, continued recognition of etiologic agents in occupational and nonoccupational exposures is important, because knowledge of these agents not only allows better diagnosis and patient management but also leads to abatement of the exposures. These contextual associations are recognized in the names of various forms of HP, among which are *farmer's lung*, *bird-breeder's disease*, and *ventilation pneumonitis*. However, it is likely that types of HP exist that have not yet been recognized and described.

The prevalence of causative agents varies greatly within and between countries as well as with seasonal changes.[45] For example, the most prevalent form of HP in dairy-farming areas of the midwestern United States is farmer's lung.[46,47] (This is actually a disease of dairy farmers; grain farmers are not affected). However, patients from different farming areas react to different species of thermophilic actinomycetes.[48] The most prevalent form of HP in southern Japan is the summer type that is caused by seasonal mold contamination in homes with *Trichosporon cutaneum* or *Cryptococcus albidus*.[49,50] In one Japanese nationwide survey, this entity accounted for 74.4% of all cases of HP.[50] In Tokyo, however, only one third of cases were summer-type HP.[24]

Of the many people exposed to potential etiologic agents, only a few develop HP. In farming communities, the prevalence of farmer's lung ranges from fewer than 1% to 6% of the farmers.[46,51] In a survey of 200 pigeon-breeders, Fink et al[52] detected the presence of precipitating antibodies to pigeon antigens in 40% of subjects and interstitial infiltrates on chests radiography in 5% of all breeders.

In some patients HP might be a reaction to a single environmental agent, whereas in other patients the lung disease might represent a reaction to a number of inhaled antigens, no one of which is responsible for the disease in all cases. One example of a complex environment containing many organisms is a dairy barn (several species of thermophilic actinomycetes, *Aspergillus fumigatus*, and storage mites).[48,53] Another example is the complex ecosystem that can be found in a contaminated humidifier system (bacteria such as *Klebsiella* species and many molds, such as *Aureobasidium*, *Chaetomium*, *Pullularia*, *Cephalosporium*, *Curvularia*, and *Penicillium* species; in industrial cold mist humidifiers, amebae and mites). Small amounts of these humidifier antigens also occur in soil, lake water, and outdoor air in the summer.[54-57] Even in the context of a specific exposure, there can be several potential antigens that might be triggering the inflammatory lung disease.[58] This is illustrated the instance of bird-fancier's disease, in which the inciting bird-related antigens might include immunoglobulins, intestinal mucin (which is present in bird droppings), or blooms (a waxy substance that coats the feathers of birds).[59,60] Although the antigens that bind to IgG also cause the acute reaction,[61] the antigens that react directly with lymphocytes can be quite restricted.[60]

TABLE I. Causative agents of hypersensitivity pneumonitis

Agent*	Source	Disease
Microbes		
Thermophilic actinomycetes	Moldy plant materials	Farmer's lung
Saccharopolyspora rectivirgula (Micropolyspora faeni)	Moldy hay	
Thermoactinomyces vulgaris	Moldy hay, compost	Farmer's lung, mushroom-worker's lung, composter's lung
Thermoactinomyces sacchari	Sugar cane residue	Bagassosis
Bacillus subtilis	Detergent enzymes	Detergent-worker's lung
Aspergillus clavatus	Moldy grains	Malt-worker's lung
Aspergillus versicolor	Animal bedding	Dog house disease
Aspergillus species	Tobacco mold	Tobacco-worker's lung
Penicillium casei	Cheese mold	Cheese-washer's lung
Penicillium frequentans	Moldy cork	Suberosis
Penicillium chrysogenum	Moldy wood dust	Woodworker's lung
Cryptostroma corticale	Moldy maple bark	Maple bark–stripper's lung
Aureobasidium pullulans	Moldy sequoia dust	Sequoiosis
Aureobasidium species	Contaminated water	Sauna-taker's disease
Alternaria species	Wood or wood pulp	Woodworker's lung
Merulius lacrymans	—	Dry rot lung
Botrytis cinerea	Grape mold	Winegrower's lung or Späetlase lung
Trichosporon cutaneum	Mold in Japanese homes	Summer-type HP
Cephalosporium	Sewage	Sewage-worker's lung
Mucor stolonifer	Paprika	Paprika-splitter's lung
Candida albicans	Saxophone mouthpiece	Sax lung
Mycobacterium avium-intracellulare	Contaminated water	Hot tub lung
Mixed ameba, fungi, and bacteria	Cold mist and other humidifiers, air conditioners	Nylon plant or office worker's or air conditioner's lung, ventilation pneumonitis
Bacteria and fungi	Contaminated metal-working fluids	Machine-operator's lung
Animals		
Avian proteins	Bird excreta, blood, or feather	Bird-breeder's lung, bird-fancier's lung, pigeon-breeder's lung
Rat proteins	Rat urine or serum	Rodent-handler's lung
Gerbil proteins	Gerbil	Gerbil-keeper's lung
Animal fur protein	Animal fur	Furrier's lung
Ox and pork protein	Pituitary snuff	Pituitary snuff–taker's lung
Mollusk shell protein	Mollusk shell dust	Oyster shell lung
Fish	Fish meal dust	Fishmeal-worker's lung
Wheat weevil	Flour	Miller's lung
Silk worm larvae proteins	Silk worm larvae	Sericulturist's lung
Plants		
Soybean	Soybean hulls	Soybean-worker's lung
Coffee	Coffee bean dust	Coffee-worker's lung
Lycoperdon species	Puffballs	Lycoperdonosis
Chemicals		
Isocyanates	Paints, plastics	Paint-refinisher's lung
Anhydrides	Plastics	Chemical-worker's lung, plastic-worker's lung, epoxy-worker's lung
Pauli's reagent	—	Pauli's reagent lung
Bordeaux mixture	Vineyard fungicide	Vineyard-sprayer's lung
Pyrethrum	Insecticides	Insecticide lung
Metals		
Cobalt	—	Hard metal lung disease
Beryllium	—	Berylliosis

*The more frequent causative agents are listed in bold type.

CLINICAL MANIFESTATIONS

Except for fever and acute-phase reactions after heavy exposure, the clinical features of HP are limited to the respiratory system; the symptoms and signs at presentation are nonspecific.[62] Practically, HP can present in an acute, a subacute, or a chronic form. Short-term, high-level exposure tends to cause acute disease, whereas per-

sistent low-level exposure tends to cause more chronic disease. The acute, high-intensity exposure often produces an acute influenza-like condition or respiratory distress with dyspnea, nonproductive cough, fever, chills, and myalgias occurring 4 to 48 hours after exposure to the causative antigen.[63] Symptoms and clinical features usually improve quickly after avoidance of further exposure to the inciting agent. In subacute HP, an insidious onset of exertional dyspnea, fatigue, and cough can occur several days to weeks after exposure, with few if any initial symptoms. The patient might have a subacute or chronic course, interspersed with acute exacerbations, often related to intermittent or seasonal exposure to the antigen(s). The exacerbations might coincide with returning to work and subside when the patient is away from the offending environment or on vacation and removed from the usual setting for an extended period. Low-level, chronic exposure over several months can result in even more insidious respiratory symptoms with dyspnea, cough that might be associated with mucopurulent sputum, weight loss, and anorexia. The chronic pattern is often indistinguishable from other forms of fibrotic pulmonary disease, though clubbing is uncommon. The chronic stage often portends progressive and irreversible disease despite further avoidance of exposure to the inciting agent and treatment with corticosteroids.

DIAGNOSIS

Because of its relatively low incidence in the general population, HP often goes unrecognized and is frequently misdiagnosed as respiratory infection or idiopathic interstitial lung disease, depending on the mode of clinical presentation.[64] This variability in the clinical presentation of HP is likely to lead to underdiagnosis of the condition unless it is considered as a diagnostic possibility in a number of different clinical settings. For example, it is not uncommon for bird-fancier's disease to present with insidious onset of persistent cough and slowly progressive exertional dyspnea rather than intermittent acute symptoms after exposure. In some patients, respiratory symptoms dominate the clinical presentation, whereas in others, systemic symptoms overshadow other manifestations. These symptoms, when present, might be intermittent, corresponding to episodic exposures to the inciting agent, or might be chronically present, as in chronic HP. Even when a specific exposure is recognized as the source of lung disease, the disease might not be HP. For example, exposure to farm dust can cause a variety of other immunologically mediated responses to storage mites, cow dander, endotoxin, and pesticides.[65]

As is true for many diseases, the diagnosis of HP will not be made if the diagnostic possibility is not entertained in the first place. This diagnosis is unlikely to be missed if the possibility of occupational or environmental cause is routinely considered in the differential diagnosis of any patient with a respiratory problem. Once the suspicion of HP arises on the basis of initial history-taking, a thorough occupational and environmental history must follow. This should include a search not only to identify a possible causative agent but also to establish a temporal relationship between environmental exposures and initial onset of symptoms as well as episodic clinical manifestations.

There is no single radiologic, physiological, or immunologic test specific for the diagnosis of HP. The diagnosis is often suspected when there is evidence of a respiratory disease in combination with a history of relevant environmental or occupational exposure. Respiratory symptoms of radiographic infiltrates of an episodic nature—eg, "recurrent pneumonia"—should also raise the suspicion of HP. The suspicion is strengthened when there is a temporal relationship between symptoms and occupational or environmental exposure.

Physical examination is unlikely to be helpful in establishing the diagnosis of HP, but the presence of crackles and (sometimes) wheezing or other adventitial sounds is expected on auscultation of the lungs. Clubbing is uncommon. Unexpected extrapulmonary findings might eventually lead to other diagnoses.

Routine laboratory tests are generally not helpful. The erythrocyte sedimentation rate and leukocyte count might be moderately elevated, particularly in acute HP. Total IgG is elevated, and the rheumatoid factor is often positive. Peripheral eosinophil count and serum IgE concentration are generally normal.

Specific serum precipitating antibodies are found in many, though not all, patients with HP.[64,66] Precipitating antibodies might not be demonstrable in some patients because of the insensitivity of the test or, more often, because of failure to include the causative antigen. It should also be noted that as many as 40% to 50% of asymptomatic individuals exposed to the same antigens will also have IgG antibodies in their serum.[52,64,67-69] Thus the presence of serum precipitins against suspected antigens indicates past exposure sufficient to elicit a humoral immunologic response but not necessarily sufficient to bring on the disease. For the diagnosis of HP, the precipitin test is reasonably sensitive, but it is nonspecific and should be ordered selectively. Skin tests might also demonstrate nonspecific positivity and are not helpful in the diagnosis of HP.[70] Cell-mediated hypersensitivity to the presumptive antigen, as shown by the presence of specific sensitized T cells, might be more reliable in distinguishing patients with HP from asymptomatic exposed counterparts.[60]

Chest radiography and high-resolution computed tomography (HRCT) of the chest can provide supportive evidence as to the underlying diagnosis. Radiographic findings will vary according to the stage of the disease.[71-73] In acute HP, bilateral micronodular (1-4 mm in diameter) infiltrates or patchy ground-glass opacities are usually seen and are better demonstrated with HRCT (Fig 1).[74,75] HRCT might also demonstrate decreased attenuation (air trapping caused by associated bronchiolitis) and mosaic perfusion.[76] These features can be better illustrated on expiratory views. In the subacute stage, fine linear shadows and small nodules produce a reticulonodular appear-

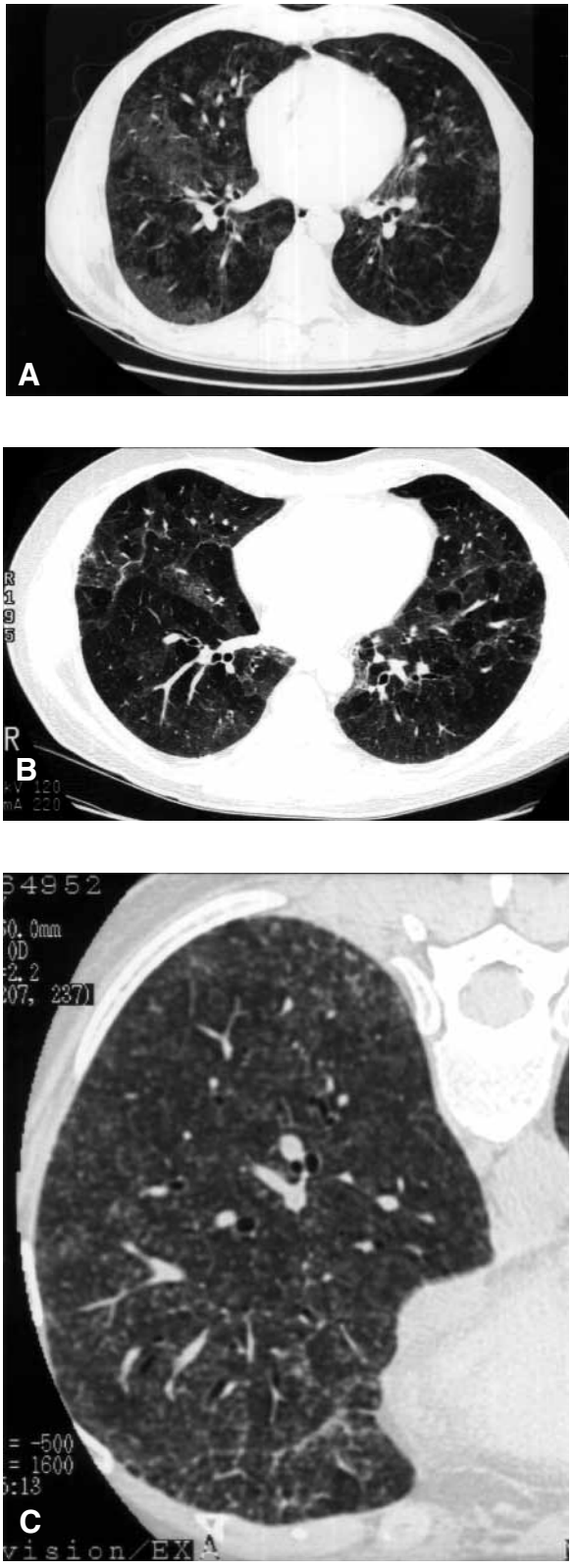

FIG 1. HRCT of the chest. **A,** Patient with HP has patchy ground-glass opacities. **B,** Patient with HP has patchy ground-glass opacities with areas of air trapping *(dark areas)* in a mosaic pattern (expiratory view). **C,** Patient with HP has diffuse micronodular infiltrates.

ance on chest radiographs. In chronic disease, chest radiography demonstrates loss of volume and reticulonodular infiltrates suggestive of interstitial fibrosis or honeycombing.[77] Commonly, these infiltrates are predominantly distributed in the upper- and mid-lung zones, which would be highly unusual for idiopathic pulmonary fibrosis. As the disease advances, further volume loss, as well as honeycombing and bronchiectatic changes, might become apparent. Pleural effusions and hilar adenopathy are rare at any stage of the disease.

Pulmonary function testing usually demonstrates restrictive changes with impaired diffusing capacity that are neither specific nor diagnostic for HP.[78] Superimposed airway obstruction might be seen with a reduced FEV_1/forced vital capacity ratio, particularly with chronic HP.[64,79] Assessment of the degree of small airways involvement and obstruction remains challenging. Arterial blood gas analysis usually reveals an increased alveolar-arterial oxygen gradient, and frank hypoxemia is seen in severe cases. Oxygen desaturation with exercise is also a clue of early gas exchange abnormalities and might be helpful in suspected cases of HP.

At this point in the diagnostic evaluation of a suspected patient, the diagnosis of HP might be sufficiently established on the basis of typical clinical features and the presence of relevant environmental exposure. When the diagnosis of HP is uncertain, additional investigation is warranted.

The usual next step in the diagnosis of HP is bronchoscopy to obtain diagnostic lung tissue and BAL fluid. Transbronchial lung biopsy samples might yield parenchymal lung tissue demonstrating features consistent with HP or another diagnosis. The histopathologic features of HP are distinctive but not pathognomonic. The characteristic histopathologic findings of HP include diffuse interstitial infiltrate, scattered noncaseating granulomas, and cellular inflammation of the bronchioles.[26] The interstitial infiltration often involves lymphocytes, macrophages, mast cells, and plasma cells. Bronchiolar obstruction might also be present. However, the histologic changes described in patients with small airways disease and adult bronchiolitis are not specific and do not show a consistent relationship to clinical, physiological, or radiographic abnormalities. Generalized vasculitis and/or necrotizing granulomata are absent. If there is severe exposure or if the exposure includes endotoxin, there might also be significant neutrophilic inflammation as well as emphysema. Whether these histopathologic features are present will depend partly on the duration or stage of the disease as well as the adequacy of the lung biopsy sample. Transpleural endoscopic lung biopsy is usually not required to establish the diagnosis but can be helpful in diagnostically challenging cases in which a larger sample is needed to examine the complex pathology. This is particularly true in cases of chronic HP in which the symptoms are of insidious onset and cannot be clearly related to any particular exposure.

BAL might provide useful supportive data in the diagnosis of HP. Analysis of BAL fluid usually reveals

intense lymphocytosis of predominantly $CD8^+$ T-suppressor cells. This is in contrast to sarcoidosis, in which BAL fluid usually demonstrates $CD4^+$ T-helper cell lymphocytosis.[64] However, BAL findings likely vary depending on the timing of the last antigen exposure and the stage of the disease. Soon after acute exposure, neutrophils predominate.[80] Later, as the disease progresses to the chronic form, the ratio of $CD4^+$ to $CD8^+$ T cells increases, and when fibrosis is present the numbers of neutrophils increase.[43,81] Smoking also affects the BAL cellular phenotype.[82]

In some instances, a careful inspection of the suspected environment with air, water, dust, or soil sample collection and analysis for antigens might be indicated, especially indoors and in the workplace.[57,83] An experienced industrial hygienist can facilitate this environmental survey process. However, even when it is properly performed, the results of environmental sampling can be difficult to interpret for clinical purposes.

Pulmonary function testing performed before and after occupational or environmental exposure might also be helpful diagnostically. Provocative testing by inhalational challenge is rarely required to make the diagnosis of HP and might precipitate a severe exacerbation.[78,84] Inhalational challenge is generally performed in the hospital setting where acute, severe attacks can be appropriately managed.

A committee of the American Academy of Allergy, Asthma and Immunology has proposed criteria for diagnosis.[78] Recently, Schuyler and Cormier[66] have formalized these criteria (Table II). The diagnosis is considered confirmed if the patient fulfills 4 of the major criteria and at least 2 of the minor criteria and if all other disease with similar symptoms and signs have been excluded. Although these criteria provide useful guidelines with regard to the diagnosis of the disease, strict clinical application of the criteria appears unwarranted.

Table III lists the diseases to consider in the differential diagnosis.

TABLE II. Diagnostic criteria for hypersensitivity pneumonitis*

Major criteria
1. History of symptoms compatible with hypersensitivity pneumonitis that appear or worsen within hours after antigen exposure
2. Confirmation of exposure to the offending agent by history, investigation of the environment, serum precipitin test, and/or bronchoalveolar lavage fluid antibody
3. Compatible changes on chest radiography or high-resolution computed tomography of the chest
4. Bronchoalveolar lavage fluid lymphocytosis, if bronchoalveolar lavage performed
5. Compatible histologic changes, if lung biopsy performed
6. Positive "natural challenge" (reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment) or by controlled inhalational challenge

Minor criteria include:
1. Basilar crackles
2. Decreased diffusion capacity
3. Arterial hypoxemia, either at rest or with exercise

*Adapted from Schuyler and Cormier.[66]

TABLE III. Differential diagnosis

Acute stage
Acute tracheobronchitis, bronchiolitis, or pneumonia
Acute endotoxin exposure
Organic dust toxic syndrome
Allergic bronchopulmonary aspergillosis
Reactive airways dysfunction syndrome
Pulmonary embolism/infarction
Aspiration pneumonitis
Bronchiolitis obliterans organizing pneumonia
Diffuse alveolar damage
Subacute stage
Recurrent pneumonia
Allergic bronchopulmonary aspergillosis
Granulomatous lung diseases
Infection—mycobacteria, fungi
Berylliosis
Silicosis
Talcosis
Langerhans' cell histiocytosis
Churg-Strauss syndrome
Wegener's granulomatosis
Sarcoidosis
Chronic stage
Idiopathic pulmonary fibrosis
Chronic obstructive pulmonary disease with pulmonary fibrosis
Bronchiectasis/bronchiolectasis
Mycobacterium avium complex pulmonary disease

MANAGEMENT

The mainstays of treatment of HP are early diagnosis and the avoidance of further exposure to the causative agent(s). As noted previously, accurate identification of the specific antigen remains challenging. In addition, even if early recognition of the inciting agent is made, various personal motives rather than pathogenic factors might be important in the decision to avoid a particular environment or occupation, such as farming.[85] Protective equipment, such as laminar flow high-efficiency particle arrest–filtered helmets, can be considered, but the effectiveness of such equipment has not been proved. Supportive management and a short trial of corticosteroids (eg, 2 to 4 weeks of prednisone 0.5 mg/kg/day) is appropriate in acute HP. Subacute stages of HP might require higher doses of corticosteroids for several months. The long-term beneficial effects of corticosteroids on arresting disease progression in subacute or chronic HP remain to be definitively established, however. Significant changes in industrial practice, indoor air pollution, and animal handling might be required for improving long-term outcomes from a population-based perspective, as has been the case for maple bark–stripper's disease, bagassosis, and cold mist humidifier disease in the nylon industry. Changes in the way Midwestern dairy farmers handle silage and hay has greatly reduced the frequency of farmer's lung.

TABLE IV. Key features of the stages of hypersensitivity pneumonitis

	Time frame	Clinical features	HRCT findings	Immunopathology	Prognosis
Acute	4-48 hr	Fever, chills, cough, hypoxemia, aches	Ground-glass infiltrates	Alveolitis, immune complex	Good
Subacute	Weeks to 4 mo	Dyspnea, cough, episodic flares	Micro-nodules, air trapping	Granulomas, bronchiolitis	Good
Chronic	4 mo to years	Dyspnea, cough, fatigue, weight loss	Fibrosis +/– honeycombing, emphysema	Lymphocytic infiltration and fibrosis, neutrophil-mediated air space destruction	Poor

HRCT, High-resolution computed tomography.

PROGNOSIS

The natural history of HP is only partially understood and requires further study. The prognosis seems very good if the disease is detected early and exposure to the offending agent is removed, most of the improvement being seen over the first 1 to 6 months. In the acute stages, there might be restriction with decreased static compliance and diffusing capacity that reverses over several weeks. In subacute HP, the bronchiolitis and granuloma formation might be slower to resolve, even with corticosteroids. The long-term prognosis of farmer's lung is poor.[86] In some patients, progression might continue even after further exposure is avoided. For example, 24 of 61 farmers with acute HP who stopped farming for 3 to 5 years noted continued declines in diffusion capacity of the lung for carbon monoxide and total lung capacity.[87] There appear to be several predictors of long-term decline in farmers—recurrent acute episodes, swine confinement areas, exposure to bacterial endotoxin, allergy to mites/organic dust, and fungal infections.[86,88-90] Several investigators have noted an increased risk of emphysema in farmers with HP. For example, in one case control study of 88 patients (82% nonsmokers; mean follow-up 14 years), 23% had emphysema on HRCT chest and pulmonary function testing; this compared with 7% in control farmers.[89] The chronic fibrosis stage tends to be slowly progressive and irreversible, potentially leading to respiratory failure, cor pulmonale, and death.

SUMMARY AND CONCLUSIONS

HP is the result of a cell-mediated immune response of the lung to a wide variety of inhaled antigens. The clinical features are derived from the type and duration of interaction between the inciting inhaled agent from the environment, a susceptible host, and the resulting human immune response within the microenvironment of the airways and/or pulmonary interstitial compartments. There appear to be 3 distinct phases—acute, subacute with intermittent exacerbations, and chronic—each having some unique clinical, diagnostic, and immunopathogenetic aspects (Table IV). The mainstay of diagnosis and management is a careful exposure history and further avoidance of the causative agent if it is identified. With further clarification of the eliciting agents, molecular and immunobiologic mechanisms, and staging scheme, targeted and stage-specific therapeutic strategies might also improve clinical outcomes. Because the natural history of many interstitial diseases involves progression through the same phases described for HP, knowledge about the immunopathogenesis gained from studies of this condition might provide a way to understand the causes, development, and innovative treatments of other interstitial lung diseases.[91]

Many questions about HP remain to be answered. The following are some of them:

- What is the current prevalence of HP? How often is it the cause of chronic interstitial fibrosis?
- How useful would immunochemical or PCR tests for cytokines, chemokines, CD molecules, and so forth in BAL samples or biopsy specimens be?
- Do genetic polymorphisms account for the disease? If so, what are they?
- Why do most exposed individuals develop a vigorous antibody response whereas only 1% to 5% of exposed individuals develop the disease?
- What is the cell biology of the apparent protective effect of cigarette smoking?
- What is the true importance of concomitant exposure to airborne endotoxin?
- What are optimal standardized and validated immunochemical assays for identifying antigens that cause HP?
- What are the clinical value and cost-effectiveness of environmental sampling?
- What is the long-term prognosis, especially for disease that results from antigens such as molds or from thermophilic actinomycetes that are prevalent in small concentrations in ordinary environments?

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